Thermography: High sensitivity and specificity diagnosing contact dermatitis in patch testing

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Abstract: Background Patch testing of contact allergens to diagnose allergic contact dermatitis (ACD) is a traditional, useful tool. The most important decision is the distinction between allergic and irritant reactions, as this has direct implications on diagnosis and management. Our objective was to evaluate a new method of non-contact infrared reading of patch tests. Secondary objectives included a possible correlation between the intensity of the patch test reaction and temperature change. Methods 420 positive reactions from patients were included in our study. An independent patch test reader assessed the positive reactions and classified them as allergic (of intensity + to +++) or irritant (IR). At the same time, a forward-looking infrared (FLIR) camera attachment for an iPhone was used to acquire infrared thermal images of the patch tests, and images were analyzed using the FLIR ONE app. Results Allergic patch test reactions were characterized by temperature increases of 0.72 ± 0.67 °C compared to surrounding skin. Irritant reactions only resulted in 0.17 ± 0.31 °C temperature increase. The mean temperature difference between the two groups was highly significant ($p < 0.0001$) and therefore was used to predict the type of contact dermatitis. Conclusions Thermography is a reliable and effective way to distinguish between allergic and irritant contact dermatitis. Keywords Allergic contact dermatitis Contact allergy Infrared Irritant contact dermatitis Patch testing

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Original Article

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ACD	allergic contact dermatitis
FLIR	forward-looking infrared
IR	irritant

ABSTRACT

Background: Patch testing of contact allergens to diagnose allergic contact dermatitis (ACD) is a traditional, useful tool. The most important decision is the distinction between allergic and irritant reactions, as this has direct implications on diagnosis and management. Our objective was to evaluate a new method of non-contact infrared reading of patch tests. Secondary objectives included a possible correlation between the intensity of the patch test reaction and temperature change.
Methods: 420 positive reactions from patients were included in our study. An independent patch test reader assessed the positive reactions and classified them as allergic (of intensity + to +++) or irritant (IR). At the same time, a forward-looking infrared (FLIR) camera attachment for an iPhone was used to acquire infrared thermal images of the patch tests, and images were analyzed using the FLIR ONE app.
Results: Allergic patch test reactions were characterized by temperature increases of 0.72 ± 0.67 °C compared to surrounding skin. Irritant reactions only resulted in 0.17 ± 0.31 °C temperature increase. The mean temperature difference between the two groups was highly significant ($p < 0.0001$) and therefore was used to predict the type of contact dermatitis.
Conclusions: Thermography is a reliable and effective way to distinguish between allergic and irritant contact dermatitis.

Introduction

Eczema is a frequent symptom that can be the clinical expression of allergic contact (ACD), non-allergic, irritant contact dermatitis or other inflammatory diseases. Patch testing is a valuable clinical tool for identifying culprit substance(s) in patients with suspected contact sensitization. Non-toxic substances known to have allergenic potential are applied to the back of the patient under occlusion for 48 h. Subsequently, the skin is evaluated for erythema, infiltration and vesicles/blisters. Later readings are performed at 72 h, 96 h and sometimes even later. The interpretation of the test can be challenging, requires experience, and particularly the distinction between irritant and allergic reactions can be frequently difficult to make.[1]

In some cases, irritant reactions can be difficult to distinguish from mild allergic reactions. When patch tests are removed after 48 h, the inflammation induced by irritants tends to decline within 24 h. This phenomenon is called the “decrescendo-phenomenon”. Vice versa, the intensity of inflammation caused by ACD tends to increase, a phenomenon referred to as the “crescendo-phenomenon”.

Positive patch-tests contain skin lesions that are erythematous, infiltrated and can show vesicles. The latter is in part due to vasodilation and increased local blood circulation.[2] The increased blood flow suggests that the temperature of patch test lesions may be warmer than the surrounding normal skin. Indeed, a few early studies with thermographic equipment have confirmed this

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hypothesis.[3–7] In the previous studies, erythematous, irritant lesions lead to an increased blood flow and thus to a mild increase in temperature, however allergic reactions were more intense and were characterized by a higher temperature increase, compared to surrounding skin, possibly because of a stronger vessel vasodilatation.

Recently mobile technology has produced at least two sufficiently accurate and portable solutions that technically would enable infrared patch test reading in the clinic. In consequence, we sought to study the potential utility of integrating an infrared camera in the clinical routine of patch test evaluation. Hence, this study had the purpose to evaluate if distinguishing between allergic and irritant patch test reactions is feasible by non-contact measurement of the skin temperature (thermography). The secondary objective of the study was to determine if the severity of the patch test reactions correlates to the increase of temperature.

Methods

Following informed consent (ethics commission number: KEK 2017-647), a forward-looking infrared (FLIR) camera attachment for an iPhone 6S was used to acquire infrared thermal images and standard digital images of 126 patients (Table 1) that presented to the patch testing laboratory of the University Hospital Zurich (Department of Dermatology). 79 participants were male, 47 female. On average, patients were 46 years of age ±16.6 years [18–82]. A total of 420 lesions were analyzed.

Only patients with an erythematous reaction reactions were included. 2 min after removing the occlusive patches, the infrared camera was held vertically and positioned approximately 20 cm from the skin's surface. The room temperature was steadily around 21 °C. All erythematous lesions were analyzed. Independently, a physician (who is not part of the study team) clinically evaluated the lesion (negative, IR, +, ++, +++) (Table 2).[8,9]

Assessing differences in temperature (Δt)

Then, the temperature of the lesion and the temperature of the field besides it were assessed using an infrared image analysis tool and the app FLIR ONE (Version 20.52). The differences in temperature (Δt) were compared to the clinical evaluation (Fig. 2).

Table 1
Demographics.

Total number of erythematous patch test lesions	420
Irritant contact dermatitis	166 Δt 0.17°C ± 0.31 [−1.0–1.5]*
Allergic contact dermatitis	254 Δt 0.72°C ± 0.67 [−2.8–3.3]*
allergic contact dermatitis of intensity +	153 Δt 0.54°C ± 0.47 [−0.5–3]*
allergic contact dermatitis of intensity ++	73 Δt 0.96°C ± 0.67 [−1.2–3]*
allergic contact dermatitis of intensity +++	30 Δt 1.03°C ± 1.16 [−2.8–3.3]*

Table 2
Reading criteria for patch tests according to the International Contact Dermatitis Research Group (ICDRG)[8] and the European Society of Contact Dermatitis.[9]

Symbol	Morphology	Diagnosis
–	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
IR	Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reaction

Statistical analysis and prediction of contact dermatitis

For statistical analysis, the Mann Whitney U test as well as the Kruskal Wallis test were used. The Δt values were utilized for predicting the type of contact dermatitis. There are different approaches to analyze such data, which include powerful classifiers (e.g. support vector machine). However, boosting approaches can achieve the similar classification results with much less parameter tweaking. Boosting starts with building a model from training data and keeps on creating models in order to rectify the error from previous model(s) until either the training data is perfectly predicted or the maximum number of models is reached. Therefore boosting algorithm combines the predictions of several weak learners into a strong classifier with better prediction accuracy.[10] In order to successfully predict the binary classes of contact dermatitis, an adaptive boosting classifier was developed using the AdaBoost method of R package caret.[11]

Results

Out of 420 lesions, 166 were clinically diagnosed as irritant contact dermatitis and the remaining 254 as allergic contact dermatitis of various degrees. The difference in temperature between a patch test clinically classified as an irritant reaction (Fig. 1) compared to adjacent, the mean change of temperature (Δt) of irritant skin was 0.17 °C ± 0.31 [-1.0–1.5]. Patch tests classified as allergic reactions (Fig. 2) were warmer (mean $\Delta t = 0.72$ °C ± 0.67 [-2.8–3.3]). Weak positive reactions (+) had on average a change in temperature of 0.54 °C ± 0.47 [-0.5 - 3], strong positive reactions (++) showed an increase in temperature on average of 0.96 °C ± 0.67 [-1.2 - 3] and extreme positive reactions (+++) were 1.03 °C ± 1.16 [-2.8–3.3] warmer than the surrounding non affected skin. Thermography revealed that the temperature of patch test lesions did correlate with the intensity of the allergic lesions, with the exception of strong (++) and extreme strong (+++) reactions (Fig. 3A).

The Δt between irritant and allergic lesions was highly significant ($p < 0.0001$). Therefore, an adaptive boosting classifier was built using these Δt values. Multiple performance metrics were selected to evaluate the classifier's performance. The area under receiver operating characteristic (ROC) curve (Fig. 3B) of 0.85 indicated high discriminative power of the classifier.

Also overall sensitivity and specificity of the classifier were 0.84 and 0.83 respectively which portrayed how effectively

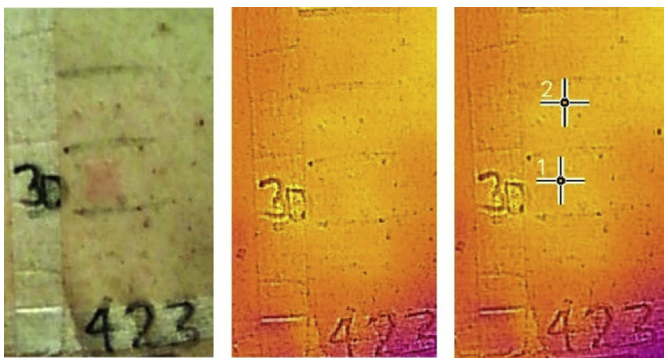

Fig. 1. Irritant reaction to sodium dodecyl sulfate (irritant lesion) showing a minor increase in temperature of 0.1 °C (1) clinical picture, 2) infrared picture 3) measurement of temperature difference).

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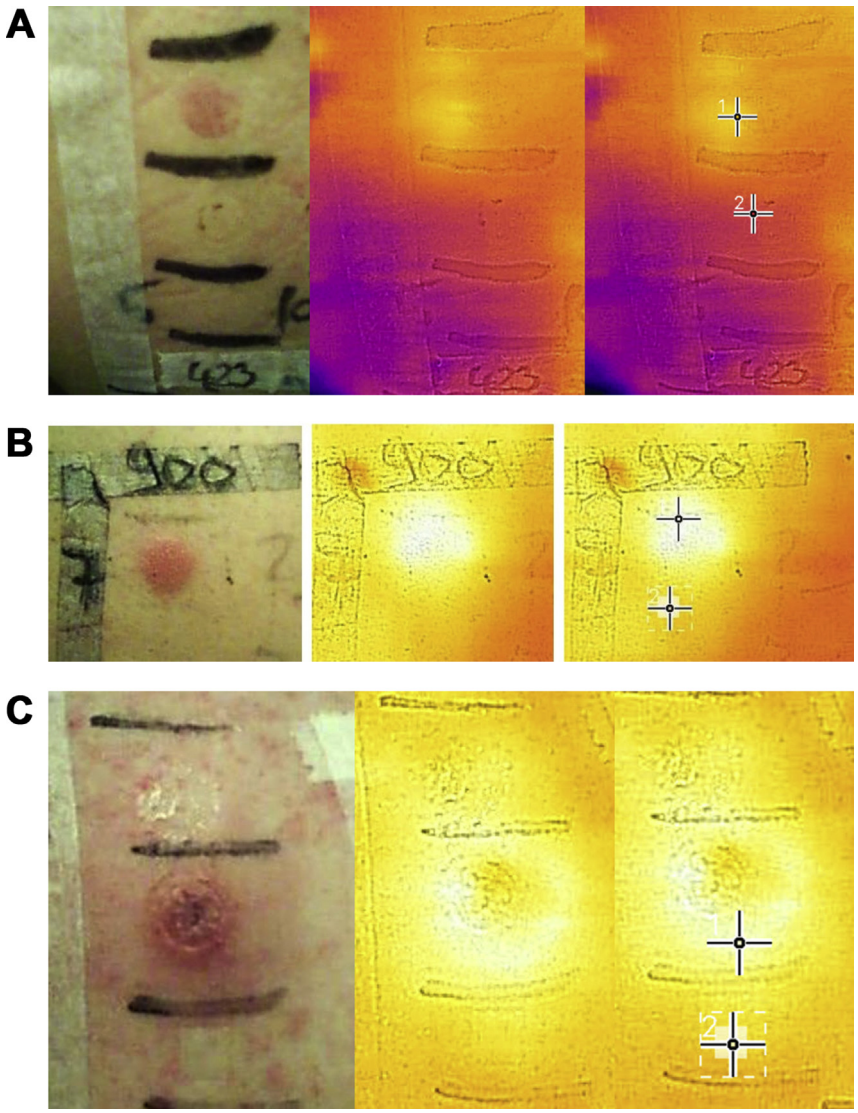

Fig. 2. A: Weak positive (+) allergic reaction to Cobalt (III) chloride with a difference in temperature (Δt) of 0.6 °C (1) clinical picture, 2) infrared picture 3) measurement of temperature difference). **B**: Strong positive (++) allergic reaction to N,N′-Dicyclohexylcarbodiimide revealing a 0.9 °C increase in temperature (1) clinical picture, 2) infrared picture 3) measurement of temperature difference). **C**: Extreme strong positive (+++) allergic reaction to p-Phenylenediamine (Δt = 0.9 °C) (1) clinical picture, 2) infrared picture 3) measurement of temperature difference).

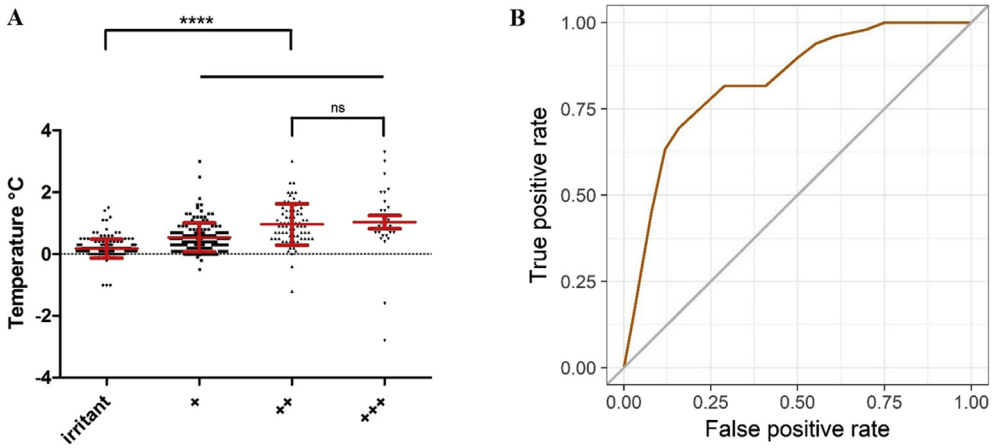

Fig. 3. A: Kruskal Wallis Test. Significant ($p < 0.0001$) change in temperature (Δ) in temperature between irritant and allergic (+, ++, +++) reactions. There was not statistical difference in temperature change between strong (++) and extremely (+++) strong allergic reaction. **B**: ROC Curve showing the predictive power of the classifier (Area under ROC curve = 0.85). True positive rate indicates the proportion of allergic contact dermatitis cases that are correctly predicted. False positive rate indicates the proportion of irritative contact dermatitis cases that are incorrectly predicted.

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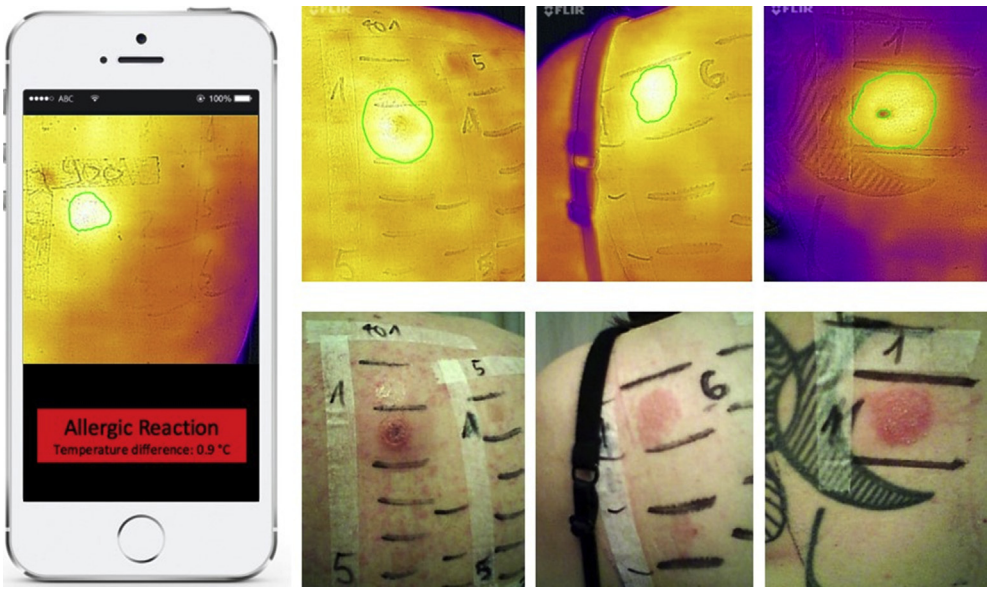

Fig. 4. Automatic allergic reaction detection. The local temperature increase is localized with image segmentation method and visualized with a green boundary. Left: a) Example FLIR App user interface. Right: FLIR images with example segmentations and corresponding clinical images. b) p-Phenylendiamine (+++), c) Cobalt (II)-chloride (+), d) Cobalt (II)-chloride (+).

thermography of patch tests can be used to predict the type of contact dermatitis.

Discussion

This study was designed to characterize a non-contact method for the thermal reading (thermography) of patch tests, and to identify the potential for unbiased objective distinction between irritant and allergic patch test reactions. As this distinction is often challenging even for experienced clinicians, it has the potential to be developed and used as a reliable, evaluator-independent and cost-effective tool for patch test reading and decision support. The area under ROC curve, sensitivity and specificity of the prediction tool have already been shown to be an indicator for the same (Fig. 3). Such a non-contact imaging technique, as studied here for thermography, may enable unbiased and higher-throughput reading and documentation in electronic patient files of patch tests when coupled to standardized positioning of contact allergens on the back of patients.

Our study showed that allergic patch test reactions are significantly warmer than irritant reactions. As mild (+) and severe (+++) reactions lead to the same diagnosis of contact allergy with similar consequences, in clinical practice differences between both degrees of reaction have no relevance. Our study also highlighted that this temperature d,ifference can successfully distinguish between allergic and irritant reactions.

However, the overall skin surface temperature is location-dependent. Therefore, only a relative difference between the site of the patch test reaction and the surrounding skin was used to determine the outcome, and not the absolute temperature of each patch test.

In dermatology, infrared thermography has been used in localized scleroderma,[12–14] systemic sclerosis,[15] hemangiomas[16] and hidradenitis suppurativa.[17] All publications have documented promising results. One study even attempted to predict a treatment response in 63 patients with eczema of different etiologies.[18] As a next step, our boosting classifier will be integrated into the FLIR ONE app with the aim of establishing a robust procedure for automated reading of patch tests. By segmenting the FLIR images we can also automatically localize the image regions exhibiting allergic reactions (Fig. 4).

Simple thresholding of FLIR image values, which corresponds to selecting pixels within a chosen temperature interval, mostly leads to noisy disconnected regions. Better results can be achieved with segmentation methods which favor compact segmentation regions.[19,20] Taken together, our results suggest that infrared imaging has the potential to be a useful, innovative and promising tool for standardized examinator independent evaluation of patch tests.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

FAn designed the study, collected samples, wrote the majority of the manuscript, approved the final version. FAl, LSK and JTM collected samples, was involved in writing and reviewing the manuscript, approved the final version. AG and MRO performed statistical analysis, was involved in writing and reviewing the manuscript, approved the final version. BM collected samples, performed statistical analysis, was involved in writing and reviewing the manuscript, approved the final version. LEF was involved in writing and reviewing the manuscript, approved the final version. MB and AAN designed the study, was involved in writing and reviewing the manuscript, approved the final version.

References

1. Ivens U, Serup J, O'Goshi K. Allergy patch test reading from photographic images: disagreement on ICDRG grading but agreement on simplified tripartite reading. *Skin Res Technol* 2007;**13**:110–3.
2. Gonzalez S, Gonzalez E, White WM, Rajadhyaksha M, Anderson RR. Allergic contact dermatitis: correlation of in vivo confocal imaging to routine histology. *J Am Acad Dermatol* 1999;**40**:708–13.
3. Laino L, Di Carlo A. Telethermography: an objective method for evaluating patch test reactions. *Eur J Dermatol* 2010;**20**:175–80.
4. Baillie AJ, Biagioni PA, Forsyth A, Garioch JJ, McPherson D. Thermographic assessment of patch-test responses. *Br J Dermatol* 1990;**122**:351–60.
5. Serup J. Contact thermography–towards the Sherlock Holmes magnifying glass for solving allergic and irritant patch test reactions? *Contact Dermatitis* 1987;**17**:61–2.

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6. Agner T, Serup J. Contact thermography for assessment of skin damage due to experimental irritants. *Acta Derm Venereol* 1988;**68**:192–5.
7. Stuttgen G, Flesch U, Witt H, Wendt H. Thermographic analysis of skin test reaction using AGA thermovision. *Arch Dermatol Res* 1980;**268**:113–28.
8. Fregert S. *Manual of Contact Dermatitis*. Copenhagen: Munksgaard; 1974.
9. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis* 2015;**73**:195–221.
10. Freund YSRE. *Experiments with a new boosting algorithm*. 13th International Conference on Machine Learning; 1996;148–56.
11. Kuhn M. Building predictive models in R using the caret package. *J Stat Softw* 2008;**28**:1–26.
12. Howell KJ, Lavorato A, Visentin MT, Smith RE, Schaefer G, Jones CD, et al. Validation of a protocol for the assessment of skin temperature and blood flow in childhood localised scleroderma. *Skin Res Technol* 2009;**15**:346–56.
13. Weibel L, Howell KJ, Visentin MT, Rudiger A, Denton CP, Zulian F, et al. Laser Doppler flowmetry for assessing localized scleroderma in children. *Arthritis Rheum* 2007;**56**:3489–95.
14. Garcia-Romero MT, Randhawa HK, Laxer R, Pope E. The role of local temperature and other clinical characteristics of localized scleroderma as markers of disease activity. *Int J Dermatol* 2017;**56**:63–7.
15. Nowicka D. Thermography improves clinical assessment in patients with systemic sclerosis treated with ozone therapy. *Biomed Res Int* 2017;**2017**:5842723.
16. Garcia-Romero MT, Chakkittakandiyil A, Pope E. The role of infrared thermography in evaluation of proliferative infantile hemangiomas. Results of a pilot study. *Int J Dermatol* 2014;**53**:e216–7.
17. Polidori G, Renard Y, Lorimier S, Pron H, Derruau S, Taiar R. Medical Infrared Thermography assistance in the surgical treatment of axillary Hidradenitis Suppurativa: a case report. *Int J Surg Case Rep* 2017;**34**:56–9.
18. Dzhevaga VN. [Infrared thermography in the diagnosis and assessment of treatment efficacy in patients with eczema nad allergic dermatitis]. *Lik Sprava* 1992:95–8 [in Russian].
19. Unger M, Pock T, Trobin W, Cremers D, Bischof H. TVSeg - interactive total variation based image segmentation. *BMVC* 2008:1–10.
20. Boykov YY, Jolly MP. Interactive graph cuts for optimal boundary region segmentation of objects in n-d images. *ICCV* 2001;**1**:105–12.

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